Routes to Mitomycins. New Syntheses of the 2,3,5,8-Tetrahydro-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indole Ring System. An Efficient Synthesis of 7-Methoxymitosene

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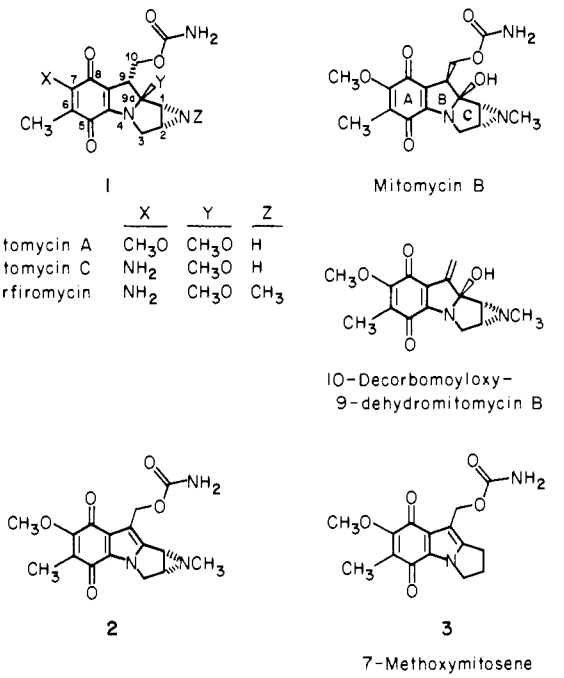
Abstract: The efficient synthesis of 7-methoxymitosene (**3**), a synthetic analogue of the mitomycins, is presented. Key steps include regiospecific addition of homoproline ethyl ester to 2,3-dibromo-5-methoxy-6-methylbenzoquinone (**7**) and photochemical introduction of both a side chain double bond and ring closure. Thus, synthesis of the target hydroxymethylindoloquinone, mitosene **18**, is accomplished with six isolations and three purifications in 30% overall yield. An alternate, nonphotochemical synthesis of the ring-closure precursor **11** consists of 4-aminobutyric acid addition to dibromoquinone **7** followed by homologation of the amine adduct to a 3-oxo-6-aminocaproate and reductive closure of the pyrrolidine ring. Oxidative demethylation of trimethoxyindole ester **14** gives the *o*- or *p*-indoloquinone as the major product, depending on the reagent used. Regioisomeric indoloquinones are obtained directly by the addition of vinylogous carbamate **25** to dibromoquinone **7** followed by metal-catalyzed ring closure.

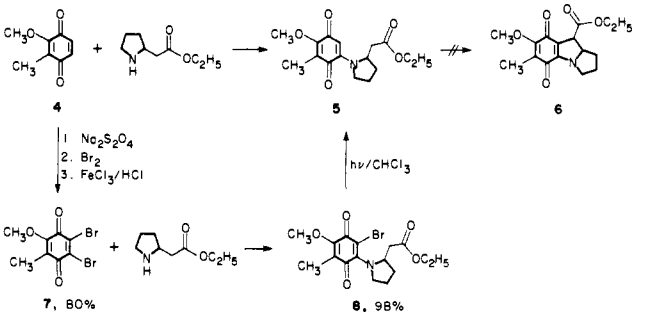
The isolation, structure, chemistry, pharmacology, biosynthesis, and synthetic studies of the mitomycin antitumor antibiotics **1** and analogues (Chart I) have been thoroughly reviewed.[1] Elimination of the functionality at C-9a in the mitomycins provides a class of compounds known as mitosenes. Aziridinomitosene **2**, obtained in this way from mitomycin B or *N*-methylmitomycin A, retains much of the strong antibiotic antitumor activity of the parent compounds.[2] Recently we reported[3] the use of iminium salts in a high-yield synthesis of 7-methoxymitosene **3**,[4] a mitomycin analogue possessing significant antibacterial activity in vitro and in mice.[4a] With continued interest in this class of compounds we sought further efficient syntheses of compounds containing the ABC ring system.

One highly convergent approach[5] failed when aminoquinone **5**, prepared by oxidative amination of quinone **4** with homoproline ethyl ester, could not be oxidatively cyclized to **6** under a variety of conditions (Scheme I). This failure can be rationalized in part by the deactivating vinylogous amide nature of aminoquinones; such an influence has thwarted other nucleophilic additions at the 3-position of 2-amino-1,4-quinones.[6] Postulating that quinone **6** alternatively might be obtained from an intramolecular addition–elimination cyclization, we embarked on the synthesis of aminobromoquinone **8**.

Chart I. Mitomycins and Mitosene Analogues



Scheme I. Routes to Aminoquinones 5 and 8



The preparation of **8** by amination of dibromoquinone **7** followed directly from our experience with the analogous pyrrolidine addition reaction.[7] In this way **8** was obtained as a single isomer in high yield. Quinone **7** is most conveniently synthesized in one

(1) (a) Most of the literature to mid 1981 is noted in ref 3. (b) General review on mitomycin C: Crooke, S. T. "Cancer Chemotherapy"; Crooke, S. T.; Prestayko, A. W., Eds.; Academic Press: New York, 1981; Vol. 3, p 49. (c) Biosynthesis: Anderson, M. G.; Kibby, J. J.; Rickards, R. W.; Rothschild, J. M. *J. Chem. Soc., Chem. Commun.* **1980**, 1277. (d) Mass spectra of synthetic mitosenes: Hodges, J.; Schram, K. H.; Baker, P. F.; Remers, W. A. *J. Heterocycl. Chem.* **1982**, *19*, 161. (e) Mitomycin analogues: Hodges, J. C.; Remers, W. A.; Bradner, W. T. *J. Med. Chem.* **1981**, *24*, 1184. (f) Recent approaches to the mitomycins: Danishefsky, S.; Regan, J. *Tetrahedron Lett.* **1981**, *22*, 3919. Danishefsky, S.; Regan, J.; Doehner, R. *J. Org. Chem.* **1981**, *46*, 5255. Naruta, Y.; Arita, Y.; Nagai, N.; Uno, H.; Maruyama, K. *Chem. Lett.* **1982**, 1859. (g) Synthesis of naturally occurring 10-(decarboamyloxy)-9-dehydromitomycin B and its analogues: Urakawa, C.; Tsuchiya, H.; Nakano, K.; Nakamura, N. *J. Antibiot.* **1981**, *34*, 1152. (h) DNA and nucleic acid alkylation with mitomycin C: Hashimoto, Y.; Shudo, K.f Okamoto, T. *Tetrahedron Lett.* **1982**, *23*, 677. Tomasz, M.; Lipman, R. *Biochemistry* **1981**, *20*, 5056.

(2) (a) Kinoshita, S.; Uzu, K.; Nakano, K.; Shimizu, M.; Takahashi, T.; Matsui, M. *J. Med. Chem.* **1971**, *14*, 103. (b) Kinoshita, S.; Uzu, K.; Nakano, K.; Takahashi, T. *ibid.* **1971**, *14*, 109. (c) Patrick, J. P.; Williams, R. P.; Meyer, W. E.; Fulmor, W.; Cosulich, D. B.; Broschard, R. W.; Webb, J. S. *J. Am. Chem. Soc.* **1964**, *86*, 1889.

(3) Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1982**, *47*, 2404.

(4) For other syntheses of **3**, see: (a) Allen, G. R.; Poletto, J. F.; Weiss, M. J. *J. Am. Chem. Soc.* **1964**, *86*, 3877; *J. Org. Chem.* **1965**, *30*, 2897. (b) Kametani, T.; Takahashi, K.; Ihara, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1976**, 389. (c) **Note Added In Proof:** Coates, R. M.; MacManus, P. A. *J. Org. Chem.* **1982**, *47*, 4822.

(5) Mandell, L.; Roberts, E. C. *J. Heterocycl. Chem.* **1965**, *2*, 479.

(6) (a) Falling, S. N.; Rapoport, H. *J. Org. Chem.* **1980**, *45*, 1260. (b) Cajipe, G.; Rutolo, D.; Moore, H. W. *Tetrahedron Lett.* **1973**, 4695.

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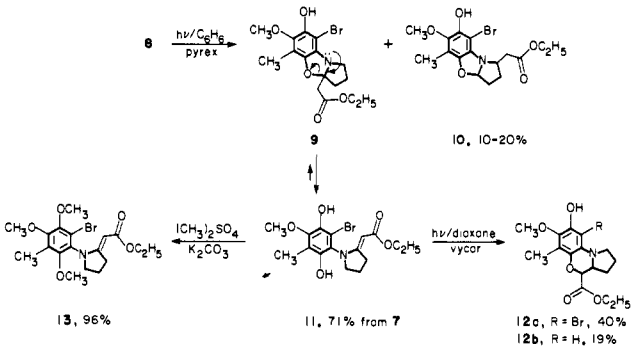
Scheme II. Photochemical Synthesis and Reactions of Hydroquinone 11



operation by dithionite reduction of quinone **4**, dibromination of the resulting hydroquinone, and oxidation with ferric chloride; direct dibromination of quinone **4** gives **7** contaminated with several minor products.

Bromoquinone **8**, like other aminobromoquinones,[6a,7] loses bromine when exposed to light, the loss being particularly rapid in chloroform or at elevated temperatures. Stimulated by this observation, we set aside the direct ring closure reaction and explored the photochemistry of quinone **8**. We found its behavior in benzene to be quite different. As shown in Scheme II, exposing a benzene solution of **8** to sunlight afforded vinylogous carbamate **11** as the major product accompanied by benzoxazole **10**. There is ample precedent for photochemical conversions of N-alkylaminobenzoquinones to benzoxazoles.[8] The presence of the nitrogen is not a requirement for this photoinsertion reaction, and analogous reactions of alkyl quinones and of quinones in general have been reported.[9] The formation of vinylogous carbamate **11** can be rationalized by the formation of isomeric benzoxazole **9** followed by iminium salt/phenoxide formation[10] and proton transfer.

The infrared spectrum of **11** reveals a typical vinylogous carbamate carbonyl stretching frequency at 1672 cm^{-1}. The ^1H NMR spectrum of **11** is solvent dependent. In $(CD_3)_2CO$ all absorptions are accounted for by **11**, including two sharp phenolic OH singlets. In $CDCl_3$ approximately 10% of benzoxazole **9** is present. Prominent spectral absorptions of **9** include one phenolic singlet and two unobscured doublets in the same region as and with similar coupling constants to the two protons α to the ester in quinone **23**. That the amount of **9** does not change when the NMR sample is heated at 45 °C for 15 h suggests that the equilibrium is established rapidly.

Recently, the photocyclizations of N-haloaryl-substituted enamine derivatives such as enamides[11] and vinylogous amides (enaminones)[12] have been described. Though there is no previous report of such a cyclization on a vinylogous carbamate such as **11**, the above precedent as well as its high preparative-scale yield made **11** an attractive educt for potential mitosene synthesis via photocyclization.

Table I. Photochemical Ring Closure of 13

g	concn, mM	filter	time, h	% yield[a] 14	15	13
0.21	6.3	quartz	0.50	74	24	2
0.21	6.3	vycor	0.67	84 (53, –)[b]	7	9
0.21	6.3	Pyrex	25	95	1-2	4
1.20	10	Pyrex	129	94 (59, 21)	3	3
0.43	13	vycor	1.25	85 (55, –)[b]	9	6
0.95	14	vycor	2.9	90 (49, 24)[b]	9	1

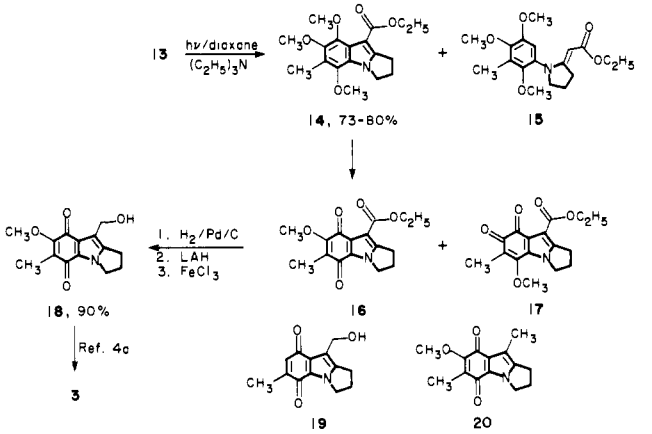
[a] Based on peak areas of cleanly separated methyl and methoxyl peaks in the expanded 250-MHz ^1H spectra. [b] Yields refer to first and second crops, when obtained, from recrystallization.

Table II. Oxidative Demethylation of 14 to *p*-Quinone 16 and *o*-Quinone 17

oxidant	reaction medium	% yield[a] 16	17
HONO	$CHCl_3$/2 M HCl/$NaNO_2$	79	9
AgO	dioxane/6 M HNO_3	41	–[b]
HNO_3	CH_2Cl_2	31	53
HNO_3	propionic acid	74[c,d]	–

[a] Yields refer to isolated products after chromatography. [b] Some **17** was formed, but it was contaminated with several uncharacterized polar compounds. [c] Not chromatographed. Estimated NMR purity 92-95%. [d] Yields varied with scale. See the text.

Scheme III. Photocyclization, Oxidation to Quinones, and Ester Reduction



Irradiation of vinylogous carbamate **11** did not furnish the desired 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole; instead, the phenol-insertion products, benzoxazines **12a** and **12b**, were formed. Reduction product **12b** is the result of photodehalogenation, a common reaction of aryl halides.[11-13] Blocking the hydroquinone as dimethyl ether **13** and subsequent irradiation did, however, give the corresponding indole **14** along with a minor amount of chromatographically similar debromination product **15** (Scheme III). Table I shows the variation in composition as a function

(8) (a) Cameron, D. W.; Giles, R. G. F. *J. Chem. Soc. C* **1968**, 1461. (b) Giles, R. G. F. *Tetrahedron Lett.* **1972**, 2253. (c) Giles, R. G. F.; Mitchell, P. R. K.; Roos, G. H. P.; Baxter, I. *J. Chem. Soc., Perkin Trans. 1* **1973**, 493. (d) Falci, K. J.; Franck, R. W.; Smith, G. P. *J. Org. Chem.* **1977**, *42*, 3317. (e) Fokin, E. P.; Prudchenko, E. P. *Izv. Sib. Otd. Akad. Nauk. SSSR, Ser. Khim. Nauk* **1966**, *2*, 98; *Chem. Abstr.* **1967**, *66*, 37809j. (f) Juodvirsis, A.; Fokin, E. P. *Izv. Sib. Otd. Akad. Nauk. SSSR, Ser. Khim. Nauk.* **1970**, 124; *Chem. Abstr.* **1971**, *74*, 3540. (g) Akiba, M.; Ikuta, S.; Takada, T. *Heterocycles* **1981**, *16*, 1579. (h) Akiba, M.; Kosugi, Y.; Okuyama, M.; Takada, T. *J. Org. Chem.* **1978**, *43*, 181; *Heterocycles* **1977**, *6*, 1773. (i) Akiba, M.; Kosugi, Y.; Takada, T. *Heterocycles* **1978**, *9*, 1607. (j) Akiba, M.; Ikuta, S.; Takada, T. *Heterocycles* **1978**, *9*, 813. (k) Akiba, M.; Takada, T. *Heterocycles* **1977**, *6*, 1861.

(9) (a) Bruce, J. M. *Q. Rev., Chem. Soc.* **1967**, *21*, 405. (b) Bruce, J. M. "The Chemistry of the Quinoid Compounds"; Patai, S., Ed.; Wiley: New York 1974; Vol. 1, pp 465–538. (c) Wedemeyer, K.-F. "Methoden der Organischen Chemie"; Georg Thieme Verlag KG: Stuttgart, 1976; Vol. 6:1c:1, pp 597–606.

(10) Such an intermediate has been used to explain the formation of other products from benzoxazole decomposition. See ref 8g.

(11) (a) Lenz, G. R. *Synthesis* **1978**, 489. (b) Ninomiya, I. *Heterocycles* **1980**, *14*, 1567. (c) Bernhard, H. O.; Snieckus, V. *Tetrahedron Lett.* **1971**, 4867. (d) Tse, I.; Snieckus, V. *J. Chem. Soc., Chem. Commun.* **1976**, 505.

(12) (a) Tiner-Harding, T.; Mariano, P. S. *J. Org. Chem.* **1982**, *47*, 482. (b) Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Org. Chem.* **1979**, *44*, 1236. (c) Iida, H.; Takarai, T.; Kibayashi, C. *J. Org. Chem.* **1978**, *43*, 975.

(13) (a) Grimshaw, J.; de Silva, A. P. *Chem. Soc. Rev.* **1981**, *10*, 181. (b) Siegman, J. R.; Houser, J. J. *J. Org. Chem.* **1982**, *47*, 2773. (c) Bunce, N. J.; Kumar, Y.; Ravanal, L.; Safe, S. *J. Chem. Soc., Perkin Trans. 2* **1978**, 880. (d) Chittim, B.; Safe, S.; Bunce, N. J.; Ruzo, L. O. *Can. J. Chem.* **1978**, *56*, 1253. (e) Bunce, N. J.; Safe, S.; Ruzo, L. O. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1607. (f) Arnold, D. R.; Wong, P. C. *J. Am. Chem. Soc.* **1977**, *99*, 3361. (g) Pinhey, J. T.; Rigby, R. D. G. *Tetrahedron Lett.* **1969**, 1267. (h) Matsuura, T.; Omura, K. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 944.

of the filter used in the irradiation. In our case, Pyrex-filtered light gave the best yield of indole **14**, but sacrificing yield for time makes the use of a vycor filter a practical alternative. These results are in contrast to those reported for the irradiation of an enaminone during which the use of vycor gave less dehalogenation than with Pyrex.[12a]

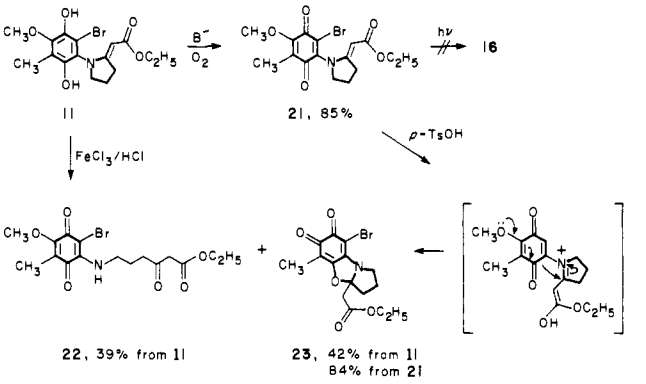
The remaining transformations in the synthesis of 7-methoxymitosene (**3**) are deblocking and oxidation of indole **14** to indoloquinone **16** followed by ester reduction to **18**; the two-step conversion (74% yield) of alcohol **18** to carbamate **3** has been reported.[4a] As observed earlier,[7] oxidative demethylation of trimethoxyarenes can lead to isomeric *p*- and *o*-methoxyquinones. Table II shows that either paraquinone **16** or orthoquinone **17** can be obtained as the major isomer, dependent on the choice of oxidant. The formation of quinone **17** represents formal entry into the unexplored orthoquinone analogues of the mitomycins. Since the two isomers are readily separated by column chromatography, the oxidative demethylation using nitrous acid[14] is the method of choice for the preparation of **16**. Nitric acid gave 92–95% pure **16** directly, but the yields (55–80%) varied with the scale of the reaction (17–150 mg).

The most common method for the conversion of indoloquinone 9-esters such as **16** to the corresponding alcohols is the hydrolysis/decarboxylation/formylation/reduction sequence[15] developed when other more direct methods either failed or gave the alcohol in poor yield.[15a] These results no doubt discouraged others from similar direct approaches. Alternatively methods via acid chlorides, prepared from the corresponding benzyl and trichloroethyl esters, have been reported. The acid chloride is then either directly reduced to the alcohol with $NaBH_4$[16] or first to the aldehyde via an intermediate thioester.[17] Three direct reductions of methyl esters to aldehyde failed,[17,18] although no analysis of the product mixtures was reported.

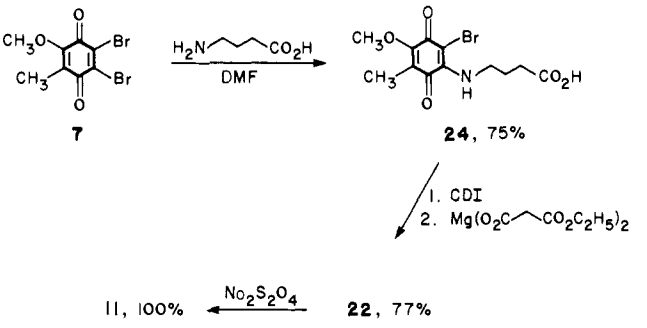
In general, the treatment of quinones with mild reducing agents gives hydroquinones while strong reductants modify the quinone in a less specific manner.[19] An efficient process would use a reagent which is just strong enough to reduce the ester without giving undesired reactions at the quinone residue. Alternatively, one could protect the quinone by reduction with a very mild reagent to the hydroquinone and then be less discriminate in the reagent used to reduce the ester. Thus, indoloquinone **16** was reduced to the hydroquinone catalytically and then treated with lithium aluminum hydride (LAH). In this way alcohol **18** was obtained after ferric chloride oxidation. Byproduct **20**, the result of overreduction, was easily removed by column chromatography, and pure **18** was isolated in 90% yield. Quinone **16** was treated with LAH directly to see if prereduction was a necessity. Though the desired alcohol **18** was formed, it was clearly the minor component (40% by NMR) of the product mixture. The major component, quinone **19** (60%), resulted from reductive loss of the quinone methoxyl. Though the quinones could not be separated by a variety of chromatographic conditions, the NMR spectrum of crude **19** clearly shows a methyl doublet split by a quinone hydrogen which appears as a quartet.[20]

The path to alcohol **18** shown in Schemes I–III proceeds in six rapid sequences from quinone **4**[7] (**4** → **7** → **11** → **13** → **14** → **16** → **18**) and uses one flask per sequence. The product of each sequence is a stable crystalline solid and only **14**, **16**, and **18** need purification. The overall yield of **18** from **4** is 30%. The previous synthesis of **18** was much more laborious and was accomplished in 18% yield via the corresponding aldehyde[3] and its reduction.[4a,c]

Scheme IV. Reactions of Hydroquinone **11**



Scheme V. Independent Synthesis of β-Keto Ester **22** and Conversion to **11**



We next considered a direct photochemical ring closure of aminoquinone **21** to indoloquinone **16** (Scheme IV). Quinone **21** is best prepared by treatment of **11** with alkali and oxygen. Irradiation of the product gave several colored compounds; no **16** was formed. Conversion of **21** to an unstable benzoxazole analogous to **10** may be among the competing processes.

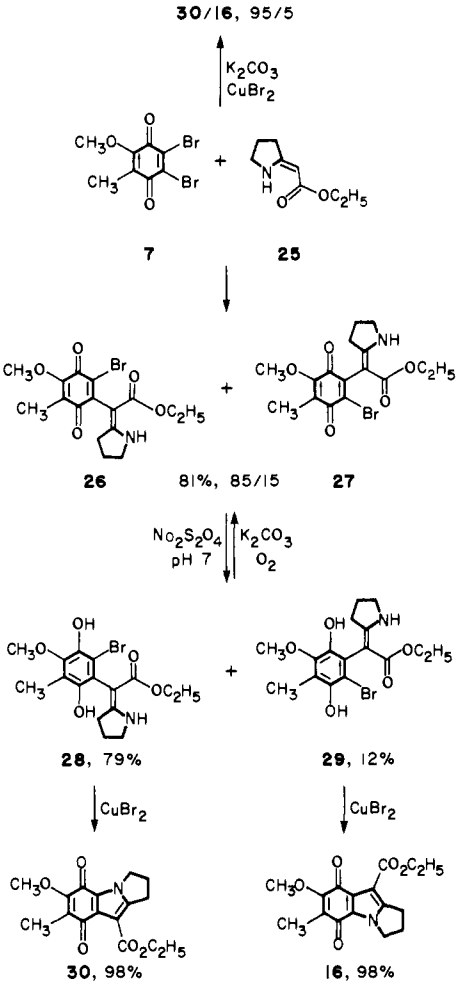
The acidic oxidation of hydroquinone **11** gives an unusual orthoquinoidal benzoxazole (**23**, 42%) as well as β-keto ester **22**, the result of the hydrolytic ring opening and oxidation. As quinone benzoxazole **23** is also produced by treatment of **21** with silica or *p*-toluenesulfonic acid, it seems likely that the ferric chloride oxidation of **11** also forms **21** which cyclizes to **23** under the acidic reaction conditions.

β-Keto ester **22** was independently synthesized by addition of 4-aminobutyric acid to dibromoquinone **7** followed by homologation of amino acid **24** by sequential treatment with carbonyldiimidazole and magnesium di(ethoxycarbonylacetate)[21,22] (Scheme V). Treating quinone **22** with dithionite effected reductive ring closure to hydroquinone **11** in quantitative yield. This sequence to **11** offers a nonphotochemical alternative to that shown in Schemes I and II. The potential of introducing asymmetry at C-1 and C-2 in the mitomycin skeleton by judicious choice of the proper 4-aminobutyric acid derivative also exists.

If a good, direct synthesis of quinone **21** were available, dithionite reduction would provide yet another route to **11**. Quinone **21** can be dissected into dibromoquinone **7** and the corresponding vinylogous carbamate **25**, but as shown in Scheme VI, carbamate **25**, prepared as reported.[23] adds at carbon rather than at nitrogen. Though quinone **27** is always the minor regioisomer, the ratio varies slightly as a function of reaction conditions. When equimolar amounts of **25** and **7** were mixed in benzene or acetonitrile in the presence of potassium carbonate, the sluggish addition (2–3 days) provided 5–8% of **27**. When carbamate **25** was treated sequentially with sodium hydride and **7** in THF, the addition went quicker (1 h) and in higher yield but was less selective (15% of **27**).

(14) Barton, D. H. R.; Gordon, P. G.; Hewitt, D. G. *J. Chem. Soc. C* **1971**, 1206.
(15) (a) Allen, G. R.; Weiss, M. J. *J. Med. Chem.* **1967**, *10*, 1. (b) *Ibid.* **1967**, *10*, 23. (c) Yamada, Y.; Yanagi, H.; Okada, H. *Agric. Biol. Chem.* **1974**, *38*, 381.
(16) Rebek, J.; Shaber, S. *Heterocycles* **1981**, *15*, 161; *Ibid. 16*, 1173.
(17) Kametani, T.; Kigawa, Y.; Nemoto, H.; Ihara, M.; Fukumoto, K. *Heterocycles* **1980**, *14*, 799.
(18) Kametani, T.; Kigowa, Y.; Nemoto, H.; Ihara, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1607.
(19) For example: Boyland, E.; Manson, D. *J. Chem. Soc.* **1951**, 1837.
(20) This characteristic pattern has been observed elsewhere; see ref 8i.
(21) Okamoto, M.; Ohta, S. *Chem. Pharm. Bull.* **1980**, *28*, 1071.
(22) Brooks, D. W.; Lu, L. D.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 72.
(23) Pinnick, H. W.; Chang, Y.-H. *J. Org. Chem.* **1978**, *43*, 4662.

Scheme VI. Vinylogous Carbamate Addition to Quinone 7; Metal-Catalyzed Ring Closures



Quinones **26** and **27** are difficult to separate, but dithionite reduction and chromatography provided pure samples of hydroquinones **28** and **29**. Ferric chloride treatment of **28** gave quantitative conversion back to **26**. The analogous reaction was not performed on hydroquinone **29**, but a pure sample of **27** was obtained by purification of a partially air oxidized sample of **29**.

The stereochemistry about the double bond in hydroquinones **28** and **29** bears close analogy to reported compounds[4b,24] in which the (*Z*)-esters, but not the (*E*)-nitriles, have an intramolecularly hydrogen bonded N–H and an upfield shift of the hetero ring C-3-hydrogens in the ^{1}H NMR spectra. (*E*)- and (*Z*)-Benzylaminocrotonates exhibit this trend as well,[24b] the implication being that the ester deshields the hetero ring C-3-hydrogens in the *E* form. Thus, the NMR spectra of *Z* isomers **25–29** ($NCH_2CH_2CH_2$, ~2.3–2.6 ppm) are quite different from those of *E* isomers **11**, **13**, **15**, and **21** (~3.3 ppm).

The regiochemistry of vinylogous carbamate addition was confirmed by conversion of hydroquinones **28** and **29** to indoloquinones **30** and **16**, respectively. Cyclization was effected by treating the hydroquinone with carbonate and cupric bromide in air. Under the alkaline conditions, the colorless hydroquinone was air oxidized to the purple quinone which was then gradually converted to the yellow indoloquinone in the presence of a metal catalyst. When **7**, **25**, carbonate, and cupric bromide were mixed, carbamate addition and ring closure occurred in one reaction; a 95/5 mixture of **30** and **16** resulted. On the same scale ferric chloride catalysis was much slower and gave about 25% conversion after 3 days; in the absence of any metal, the ring-closure reaction did not proceed. Quinones **16** and **30** were separated by MPLC on a 10-mg scale with greater than 90% mass recovery of **30**. Assuming similar reduction potentials, one might expect 6-methoxymitosene, conceivably obtainable from indoloquinone **30**, to have similar biological activity to 7-methoxymitosene.[25]

This is the first example of such a metal-catalyzed cyclization of a quinone, although there are examples of similar reactions with arenes using cuprous bromide and sodium hydride or DBU.[4b,17,18,24a] Such an intramolecular 1,4-addition to a quinone is to be contrasted with the usual mode of reactivity, 1,2-addition, that quinones such as **26** and **27** usually undergo in the Nenitzescu indole synthesis.[26] Perhaps the copper catalysis is related to the metal-catalyzed substitution of aryl and vinyl halides with imide and sulfonamide anions.[27] The role of the copper catalyst in the substitution of aryl halides with amines has been studied;[28] nickel compounds also have been used.[29]

The extension of the above photochemical and metal-catalyzed ring closures to the synthesis of 1,2-substituted mitomycin analogues is under way. In particular, derivatives of homoproline, 4-aminobutyric acid, and vinylogous carbamate **25** as chiral educts are under investigation.

Experimental Section

Reagents and solvents were distilled as follows: methanol, acetonitrile, and dimethylformamide (reduced pressure) from calcium hydride, tetrahydrofuran (THF) and dioxane from sodium/benzophenone, triethylamine (TEA) from tosyl chloride, and propionic acid neat. Potassium carbonate was crushed to a fine powder and heated at 120 °C before use.

Photochemical reactions were performed in a Hanovia-type immersion reactor with a Hanovia Hg lamp (Model 679A-368 450 W, 125–140 lamp V, 3.7 A) and with the specified filter.

Melting points are uncorrected. IR spectra were determined with Perkin-Elmer Model 137, 297, and 337 grating spectrophotometers with polystyrene film for calibration (1601.4-cm^{-1} absorption). UV spectra were determined in methanol with a Cary Model 219 spectrophotometer. ^{1}H NMR spectra were determined on the Berkeley UCB 250 (250.80 MHz) spectrometer. For complex multiplets (m) the center of the multiplet is the chemical shift which is expressed in parts per million (δ) downfield from internal tetramethylsilane. Mass spectra were obtained with AEI MS-12 (low resolution) and Du Pont CEC 21-110 (exact mass) instruments. Elemental analyses were performed by the Analytical Laboratory, College of Chemistry, University of California, Berkeley.

High-pressure liquid chromatography (HPLC) was done on an Altex analytical system consisting of two Model 110A pumps, a Model 115-10 UV–vis detector, and a Model 420 microprocessor controller/programmer using the following stainless steel Altex columns: (A) 3.2 × 250 mm, 5-μm LiChrosorb Si60 normal-phase (NP) silica gel; (B) 3.2 × 250 mm, 5-μm Ultrasphere ODS reverse-phase (RP) silica gel. Unless otherwise noted, a flow rate of 1.0 mL/min was used, with monitoring at 280 nm and with the solvent mixture described (isochratic). Preparative medium-pressure liquid chromatography (MPLC) was done with an Altex Model 110A pump equipped with a preparative liquid head and an Altex Model 151 UV detector, with monitoring at 280 nm. An Altex stainless steel column, 10 × 250 mm, 5-μm LiChrosorb Si60 silica gel (NP), was used. Column chromatography (CC) was performed with silica gel 60 (EM reagents, 63–200 μm). Analytical thin-layer chromatography (TLC) was done with aluminum-backed silica plates (E. Merck). The following chromatography solvent mixtures (v/v) were used: isooctane/ether, (A) 92.5/7.5, (B) 75/25, (C) 50/50, and (D) 40/60; acetonitrile/water, (E) 60/40 and (F) 50/50; isooctane/chloroform, (G)

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75/25 and (H) 70/30; ether/hexane, (I) 70/30; methanol/water, (J) 60/40.

Unless otherwise noted, reactions were conducted under a nitrogen atmosphere with magnetic stirring at room temperature (RT 20–26 °C) or at heating bath temperature (T_B), and final product solutions were dried over $MgSO_4$, filtered, and evaporated on a Berkeley rotary evaporator.

2,3-Dibromo-5-methoxy-6-methyl-1,4-benzoquinone (7). Quinone **4** (2.38 g, 15.6 mmol) in chloroform (80 mL) was shaken in a separatory funnel with an aqueous solution of $Na_2S_2O_4$ (11.9 g, 68.4 mmol, in 48 mL of H_2O, taken to pH 7.0 with 2 M NaOH) until the colorless hydroquinone was formed. The layers were separated, and the aqueous phase was extracted with chloroform (2 × 12 mL). The combined organic phase was dried (Na_2SO_4), filtered, and then stirred as bromine (4.36 g, 27.3 mmol, 175 mol %) in chloroform (12 mL) was added dropwise over the course of 1 min. The solvent was evaporated 20 min later, and the resulting solid was dissolved in methanol (100 mL). Ferric chloride solution (43 g $FeCl_3 \cdot 6H_2O$ in 160 mL of 0.1 M HCl) was added in one portion to the rapidly stirred methanol solution. The mixture was filtered 10 min later, and the resulting solid **7** was washed with water, dissolved in dichloromethane, dried, filtered, and evaporated to give pure **7**, identical with material prepared previously:[7] 3.45 g (71%). The filtrate, diluted with water (400 mL), was extracted with dichloromethane (3 × 55 mL), and the combined extract was washed with brine (30 mL), dried, filtered, and evaporated to provide 0.45 g (9%) more of **7**.

2-Bromo-3-[2-[(ethoxycarbonyl)methyl]-1-pyrrolidinyl]-6-methoxy-5-methyl-1,4-benzoquinone (8). To a stirred solution of homoproline ethyl ester acetate salt[6a] (0.48 g, 2.2 mmol, 140 mol %) in benzene (16 mL) was added dibromoquinone **7** (0.50 g, 1.6 mmol) and potassium carbonate (0.55 g, 4.0 mmol, 250 mol %). After 10 h the mixture was filtered into a separatory funnel, and the salts were extracted with benzene (50 mL). The combined organic phase was washed with 0.1 M H_3BO_3 (3 × 7 mL), 10% $NaHCO_3$ (7 mL), water (2 × 15 mL), and brine (1 × 15 mL). Drying (Na_2SO_4) in the dark, followed by filtration, extraction of the drying agent with a minimum amount of benzene, and evaporation provided **8** as a purple oil (0.61 g, 98%). Prolonged exposure to heat and light should be avoided; **8** is best used immediately and without further purification: R_f (CH_2Cl_2) 0.09–0.21; NMR (C_6D_6) δ 0.89 (t, 3 H, CH_2CH_3, J = 7 Hz), 1.18, 1.36, 1.95 (3 m, 1 H, 2 H, 1 H, $NCHCH_2CH_2$), 1.84 (s, 3 H, CH_3), 2.09 (dd, 1 H, $NCHCHH$, J = 8, 16 Hz), 2.43 (dd, 1 H, $NCHCHH$, J = 5, 16 Hz), 2.98 (brdd, 1 H, $NCHH$, J = 8, 12 Hz), 3.78 (s, 3 H, OCH_3), 3.9 (masked m, 1 H, $NCHH$), 3.875, 3.885 (overlapping q, 1 H each, CH_2CH_3, J = 7 Hz), 5.15 (m, 1 H, NCH); IR (neat) 2967, 1727, 1658, 1634, 1538 cm^{-1}. Anal. Calcd for $C_{16}H_{20}NO_5Br \cdot {}^1/_3H_2O$: C, 49.0; H, 5.3; N, 3.6. Found: C, 48.9; H, 5.0; N, 3.4.

Irradiation of 8. Isolation of 8-Bromo-1-[(ethoxycarbonyl)methyl]-7-hydroxy-6-methoxy-5-methyl-1,2,3,9a-tetrahydropyrrolo[2,1-*b*]benzoxazole 10 and Ethyl *N*-(2-Bromo-3,6-dihydroxy-4-methoxy-5-methylphenyl)-(*E*)-α-2-pyrrolidinylideneacetate (11). (A) With Sunlight. The amine addition to dibromoquinone **7** (0.21 g, 0.68 mmol) was carried out as above. The isolated reaction product was then diluted to 100 mL with benzene and poured into a 6-in. crystallizing dish. Swirling in bright sunlight was continued until the purple color dissipated (4 min). Evaporation of the solvent provided a white solid mixture of **10** and **11** which on trituration with solvent I provided solid **11** (0.11 g, 42%, >99% by HPLC conditions below) and a solution of **10** and **11**. Evaporation provided 0.09 g of crude which was chromatographed on 15 g of SiO_2 (solvent I) to give **10** (0.05 g, 19%, unstable oily solid which turns slightly purple upon exposure to air) and **11** (0.04 g, 15%).

10: R_f (solvent I) 0.39; NMR ($CDCl_3$) δ 1.26 (t, 3 H, CH_2CH_3, J = 7 Hz), 1.8, 2.1, 2.3 (3 m, 1 H, 1 H, 2 H, $NCHCH_2CH_2$), 2.10 (s, 3 H, $ArCH_3$), 2.47 (dd, 1 H, $NCHCHH$, J = 10, 14 Hz), 3.08 (dd, 1 H, $NCHCHH$, J = 3, 14 Hz), 3.76 (s, 3 H, OCH_3), 3.85 (br m, 1 H, NCH), 4.14 (q, 2 H, CH_2CH_3), 5.46 (s, 1 H, OH), 5.81 (dd, 1 H, $NCHO$, J = 2.5, 2.5 Hz); IR (neat) 3460, 2959, 1724, 829 cm^{-1}. Anal. Calcd for $C_{16}H_{20}NO_5Br \cdot {}^1/_2H_2O$: C, 48.6; H, 5.4; N, 3.5. Found: C, 48.9; H, 5.4; N, 3.2.

11: mp 188–189 °C; R_f (solvent I) 0.16; R_t (column B, solvent J) 9.0 min; NMR ($CDCl_3$) δ 1.22 (t, 3 H, CH_2CH_3, J = 7 Hz), 2.19 (s, 3 H, $ArCH_3$), 2.2 (m, 2 H, NCH_2CH_2), 3.1–3.6, 3.8 (2 m, 3 H, 1 H, $NCH_2CH_2CH_2$), 3.84 (s, 3 H, OCH_3), 4.07 (q, 2 H, CH_2CH_3), 4.40 (br s, 1 H, vinyl H), 5.05, 5.54 (2 br s, 1 H, 1 H, 2 OH); NMR (acetone-d_6) δ 1.13 (t, 3 H, CH_2CH_3, J = 7 Hz), 2.18 (s, 3 H, CH_3), 2.2 (masked m, 2 H, NCH_2CH_2), 3.19 (m, 2 H, $NCH_2CH_2CH_2$), 3.67 (br t, 2 H, NCH_2, J = 7 Hz), 3.81 (s, 3 H, OCH_3), 3.96 (br q, 2 H, CH_2CH_3), 4.16 (br s, 1 H, vinyl H); IR (Nujol) 3356, 2907, 1672, 1577 cm^{-1}; UV λ_{max} 279 nm (ϵ 25 850). Anal. Calcd for $C_{16}H_{20}NO_5Br$: C, 49.8; H, 5.2; N, 3.6. Found: C, 50.1; H, 5.4; N, 3.6.

(B) With Hanovia Apparatus. To a stirred solution of homoproline ethyl ester acetate salt (6.00 g, 27.7 mmol, 140 mol %) in benzene (310 mL) under nitrogen was added dibromoquinone **7** (6.00 g, 19.4 mmol) and potassium carbonate (12.00 g, 86.8 mmol, 450 mol %). After 6.5 h the mixture was filtered and the salts were extracted with benzene (90 mL). The solution was concentrated to 270 mL and two 130-mL portions of this solution were separately diluted to 190 mL, degassed with N_2 (30 min), and irradiated with Pyrex-filtered light for 25 min. Evaporation of the product mixtures to half-volume and filtration provided **11** as a white powder, 4.29 g (60% from **7**), pure by reversed-phase HPLC (as above). The filtrate was concentrated to a light purple oil which was chromatographed on 60 g of silica (solvent I) to give **11**, 0.79 g (11%), and **10**, 0.73 g (10%).

NMR Evidence for 11/9 Equilibrium. The following partial NMR data for **9** was extracted from the NMR spectrum of **11** in $CDCl_3$ solution. Benzoxazole **9** is present to the extent of approximately 10% at equilibrium, and the ratios of **11** and **9** after 15 h at 45 °C were the same as after 30 min at 23 °C. **9**: NMR ($CDCl_3$) δ 1.90, 2.43, 2.1–2.3 (m, m, masked multiplets, 1 H, 1 H, 2 H, $NCH_2CH_2CH_2$), 2.20, 2.87 (2 d, 1 H each, CH_2CO, J = 14 Hz) 5.44 (s, 1 H, OH).

Irradiation of 11. Isolation of 9-Bromo-4-(ethoxycarbonyl)-8-hydroxy-7-methoxy-6-methyl-1,2,3,3a-tetrahydro-4*H*-pyrrolo[2,1-*c*]-[1,4]benzoxazine (12a) and 4-(Ethoxycarbonyl)-8-hydroxy-7-methoxy-6-methyl-1,2,3,3a-tetrahydro-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazine (12b). Through a solution of **11** (100 mg, 0.26 mmol) and triethylamine (0.30 mL) in dioxane (100 mL) was bubbled argon with stirring. After 15 min with a continuing argon stream the stirred solution was irradiated with vycor-filtered light. After 40 min, the solvent was evaporated, and the residue was dissolved in dichloromethane (15 mL), washed with water (4 mL) and brine (4 mL), and dried (Na_2SO_4). Filtration and evaporation provided a yellow oil (110 mg) which was chromatographed on 20 g of SiO_2 (solvent I), and combination of selected fractions provided **12a** and **12b**.

12a: 40 mg (40%); R_f (ether) 0.71; NMR ($CDCl_3$) δ 1.35 (t, 3 H, CH_2CH_3, J = 7 Hz), 2.0, 2.2 (2 m, 3 H, 1 H, $NCH_2CH_2CH_2$), 2.18 (s, 3 H, $ArCH_3$), 2.65 (m, 1 H, $NCHH$), 3.30 (m, 1 H, $NCHH$), 3.78 (s, $ArOCH_3$), 3.86 (d, 1 H, OCH, J = 9 Hz), 4.2 (br m, 1 H, NCH), 4.326, 4.32 (2 overlapping q, 1 H each, CH_2CH_3, J = 7 Hz), 5.58 (br s, 1 H, OH); IR (neat) 3472, 2950, 1733 cm^{-1}. Anal. Calcd for $C_{16}H_{20}NO_5Br$: C, 49.8; H, 5.2; N, 3.6. Found: C, 50.0; H, 5.5; N, 3.5.

12b: 15 mg (19%); R_f (ether) 0.65; NMR ($CDCl_3$) δ 1.34 (t, 3 H, CH_2CH_3, J = 7 Hz), 1.7, 2.1 (2 m, 1 H, 3 H, $NCH_2CH_2CH_2$), 2.22 (s, 3 H, $ArCH_3$), 3.14 (m, 1 H, $NCHH$), 3.46 (m, 1 H, $NCHH$), 3.72 (s, 3 H, OCH_3), 3.78 (d, 1 H, OCH, J = 8.5 Hz), 4.32 (m, 2 H, CH_2CH_3), 4.3 (masked m, 1 H, NCH), 5.3 (br, 1 H, OH), 6.13 (s, 1 H, ArH); IR (neat) 3484, 2967, 1733, 1621, 1493 cm^{-1}; mass spectrum m/e (rel intensity) 309 (M + 2, 4.0), 308 (M + 1, 14.2), 307 (M^+, 48.5), 292 (100), 278 (11.1), 264 (19.4), 234 (11.0), 150 (11.4). Calcd for $C_{16}H_{21}NO_5$ m/e 307.1420, found m/e 307.1417.

Ethyl *N*-(2-Bromo-5-methyl-3,4,6-trimethoxyphenyl)-(*E*)-α-2-pyrrolidinylideneacetate (13). To a mechanically stirred solution of **11** (2.04 g, 5.20 mmol) in acetonitrile (80 mL, degassed) under argon was added powdered anhydrous potassium carbonate (3.60 g, 26.00 mmol, 500 mol %) and dimethyl sulfate (3.28 g, 2.48 mL, 26.0 mmol, 500 mol %). The mixture was heated (T_B = 50 °C) for 7 h at which time TLC (ether showed conversion of **11** (R_f 0.54) to **13** (R_f 0.68). After being briefly cooled, the mixture was filtered, the salts were extracted with acetonitrile, and the combined organic phase was evaporated to an oil. A glycine solution (12.5 g, 166 mmol, in 120 mL of water) was added to the oil, and the resulting mixture was vigorously mechanically stirred with heating (T_B = 60 °C). After being heated 1.25 h the cooled mixture was extracted with ether (3 × 40 mL) and the combined organic phase was washed with brine in $NaHCO_3$ (10 mL plus 20 mL) and then brine (10 mL). Drying, filtering, and evaporating provided **13**: 2.06 g (96%); mp 72–73 °C; R_t (column A, solvent A, 2 mL/min) 12.9 min; R_t (column B, solvent E) 18.5 min; NMR ($CDCl_3$) δ 1.21 (t, 3 H, CH_2CH_3, J = 7 Hz), 2.16 (s, 3 H, $ArCH_3$), 2.16 (masked m, 2 H, NCH_2CH_2), 3.31 (m, 2 H, $NCH_2CH_2CH_2$), 3.63 (m, 2 H, NCH_2), 3.67, 3.86, 3.88 (3 s, 3 H each, 3 OCH_3), 4.06 (q, 3 H, CH_2CH_3), 4.26 (br s, 1 H, vinyl H); IR (neat) 2976, 1686, 1635, 1458 cm^{-1}. Anal. Calcd for $C_{18}H_{24}NO_5Br$: C, 52.2; H, 5.8; N, 3.4. Found: C, 52.1; H, 5.7; N, 3.3.

Irradiation of 13. Synthesis of Ethyl 2,3-Dihydro-6-methyl-5,7,8-trimethoxy-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (14) and Ethyl *N*-(3-Methyl-2,4,5-trimethoxyphenyl)-(*E*)-α-2-pyrrolidinylideneacetate (15). (A) With Pyrex Filter. Bromide **13** (1.20 g, 2.90 mmol) was dissolved in dioxane (300 mL, degassed with argon for 1 h). Triethylamine (5.0 mL) was added and irradiation with Pyrex-filtered light was commenced as argon was bubbled through the solution. After a total of 129 h the irradiation was stopped, the solution was evaporated, and the residue was dissolved in dichloromethane (100 mL) which was washed with brine (2

× 10 mL) and dried. Filtration and evaporation provide crude **14** as an off-white solid, 1.021 g (105%), and NMR analysis showed 94% of **14**, 3% **13**, and 3% **15**. Recrystallization from ethanol–water provided pure **14**, 570 mg (59%). Concentration and chromatography (8 g SiO_2, solvent I) of the mother liquor provided more **14**, 204 mg (21%).

14: mp 125–126 °C; R_f (ether) 0.58; R_t (column A, solvent A, 2 mL/min) 29.2 min; R_t (column B, solvent F) 20.1 min; NMR ($CDCl_3$) δ 1.38 (t, 3 H, CH_2CH_3), 2.30 (s, 3 H, $ArCH_3$), 2.58 (tt, 2 H, NCH_2CH_2), 3.24 (t, 2 H, $NCH_2CH_2CH_2$, J = 7.5 Hz), 3.81, 3.88, 3.92 (3 s, 3 H each, 3 OCH_3), 4.31 (t, 2 H, NCH_2, J = 7.2 Hz), 4.34 (q, 2 H, CH_2CH_3, J = 7 Hz); IR (neat) 2959, 1709, 1493 cm^{-1}; UV λ_{max} 220 nm (ϵ 36 510), 238 (24 260), 289 (9970). Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.8; H, 7.0; N, 4.2. Found: C, 64.6; H, 7.0; N, 4.1.

15: Debrominated product **15** could only be obtained in enriched form by repeated chromatography–recrystallization sequences described above. It can be seen as a spot on TLC (solvent I) which overlaps with, but is slightly less polar than **14**; exposure of the TLC plate to iodine vapor develops **15** as a dark brown spot: NMR ($CDCl_3$) δ 1.22 (t, CH_2CH_3, J = 7 Hz), 2.1 (m, 2 H, NCH_2CH_2), 3.30 (t, 2 H, $NCH_2CH_2CH_2$, J = 7 Hz) (m, masked by impurities, NCH_2), 3.61, 3.80, 3.81 (3 s, 3 H each, 3 OCH_3), 4.06 (q, 2 H, CH_2CH_3), 4.54 (br s, 1 H, vinyl H), 6.57 (s, 1 H, ArH).

(B) With Vycor or Quartz Filters. The irradiations with vycor or quartz filters were carried out in a similar apparatus. Details of the reaction conditions and product ratios are summarized in Table I.

Oxidative Demethylation of 14. Isolation and Characterization of Ethyl 7-Methoxy-6-methyl-2,3,5,8-tetrahydro-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (16) and Ethyl 5-Methoxy-6-methyl-2,3,7,8-tetrahydro-7,8-dioxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (17). (A) With Nitrous Acid. To a stirred solution of **14** (50 mg, 0.15 mmol) in chloroform (1.2 mL) was added 3 M HCl (1.0 mL). Then sodium nitrite (75 mg, 1.1 mmol) in water (0.37 mL) was added dropwise over the course of 2.5 h. Fourteen hours later TLC (ether) showed conversion to **16** (yellow, R_f 0.71), **17** (red, R_f 0.12), and a trace of an uncharacterized compound (red, R_f 0.23). The layers were separated and the aqueous phase was extracted with chloroform until the extracts were colorless. The combined organic phase was washed with water (2 × 1 mL), dried, filtered, and evaporated to a red solid (46 mg) which was chromatographed on 1 g of SiO_2 ($CHCl_3$). Combination of selected fractions provided **16** (36 mg, 79%) and a mixture of the red products (7 mg) which was rechromatographed on 1 g of SiO_2 (ethyl acetate) to give **17** (4 mg, 9%) and R_f 0.23 material (<1 mg).

This reaction was repeated with 309 mg of **14** with a 4-h addition time and then a 16.5-h reaction time. The NMR spectrum of the crude mixture showed slightly less **17** (~5%) and slightly more of the R_f 0.23 material (~5%). Chromatography on 20 g of SiO_2 ($CHCl_3$ to remove **16** and then 5% methanol in ethyl acetate) gave pure **16** (210 mg, 75%) and a mixture of **17** and R_f 0.23 material (22 mg, ~8%).

16: mp 166–168 °C; R_t (column A, solvent G, 2 mL/min) 19.8 min; NMR ($CDCl_3$) δ 1.37 (t, 3 H, CH_2CH_3, J = 7.1 Hz), 1.94 (s, 3 H, CH_3), 2.59 (tt, 2 H, NCH_2CH_2), 3.11 (t, 2 H, $NCH_2CH_2CH_2$, J = 7.5), 4.05 (s, 3 H, OCH_3), 4.30 (t, 2 H, NCH_2, J = 7.4), 4.33 (q, 2 H, CH_2CH_3); IR ($CHCl_3$) 2985, 1724, 1675, 1647, 1613, 1502 cm^{-1}; UV λ_{max} 213 nm (ϵ 21 380), 233 (14 400), 286 (10 800), 322 (4750), 412 (740). Anal. Calcd for $C_{16}H_{17}NO_5$: C, 63.3; H, 5.6; N, 4.6. Found: C, 63.0; H, 5.6; N, 4.6.

17: mp 200–205 °C with dec; NMR ($CDCl_3$) δ 1.38 (t, 3 H, CH_2CH_3, J = 7.2 Hz), 2.02 (s, 3 H, CH_3), 2.56 (tt, 2 H, NCH_2CH_2), 3.09 (t, 2 H, $NCH_2CH_2CH_2$, J = 7.8 Hz), 4.06 (s, 3 H, OCH_3), 4.20 (t, 2 H, NCH_2, J = 7.2 Hz), 4.30 (q, 2 H, CH_2CH_3); IR ($CHCl_3$) 3003, 1727, 1689, 1664, 1608, 1563 cm^{-1}; UV λ_{max} 208 nm (ϵ 20 180), 220 (20 180), 255 (14 610), 293 (4490), 508 (1420); mass spectrum m/e (rel intensity) 306 (M + 3, 6.4), 305 (M + 2, 29.9), 304 (M + 1, 3.9), 303 (M^+, 10.5), 275 (91.6), 259 (41.6), 244 (100), 201 (39.5). Calcd for $C_{16}H_{17}NO_5$ 303.1105, found m/e 303.1099 (M^+); calcd for $C_{16}H_{19}NO_5$ 305.1263, found m/e 305.1268 (M + 2).

(B) With Argentic Oxide.[30] To a stirred solution of **14** (50 mg, 0.15 mmol) in dioxane (1.5 mL) was added AgO (75 mg, 0.60 mmol). The mixture was sonicated briefly to disperse the AgO, and then it was stirred rapidly as 6 M HNO_3 (0.15 mL) was added dropwise over the course of 0.5 min. The mixture was added to $CHCl_3/H_2O$ (6 mL/1.5 mL) after a total of 8 min, the layers were separated, and the organic phase was washed with water (1.5 mL), dried (Na_2SO_4), filtered, and evaporated to a red-orange solid (50 mg). Chromatography on 4 g of SiO_2 ($CHCl_3$) provided **16**, 18.7 mg (41%).

(C) With HNO_3/Dichloromethane.[7] To a stirred solution of **14** (50 mg, 0.15 mmol) in dichloromethane (1.6 mL) was added HNO_3/dichloromethane reagent [1.6 mL of the dichloromethane layer resulting from rapidly mixing 12 mL of dichloromethane and 3 mL of 70% (d = 1.4 g/mL) HNO_3 for 1 h]. The solution turned bright red within seconds, and after 10 min the reaction mixture was quenched with excess 10% $NaHCO_3$. The organic phase was washed with water, dried, filtered, and evaporated to a red solid (43 mg) which was chromatographed on 3 g of SiO_2 (ethyl acetate until **16** eluted and then 5% methanol in ethyl acetate). Combination of selected fractions provided **16** (14 mg, 31%) and **17** (24 mg, 53%).

(D) With HNO_3/Propionic Acid. A stirred solution of **14** (60 mg, 0.18 mmol) in propionic acid (3.75 mL) was cooled in an ethylene glycol–dry ice bath (T_B = −13 °C). After 20 min, precooled HNO_3 (3.75 mL, d = 1.4 g/mL, 70%, −13 °C) was added dropwise over the course of 1 min. The solution was stirred for 4.5 min and then was added dropwise over the course of 2 min to 5% $NaHCO_3$ (180 mL, 0–5 °C) with rapid stirring. After 5 min, dichloromethane (30 mL) was added with continued stirring, the layers were separated, and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined extracts were washed with 5% $NaHCO_3$ (10 mL) and brine (10 mL) before drying, filtering, and evaporating to a red-orange solid, 40 mg (74%). NMR ($CDCl_3$) analysis of the crude reaction mixture showed **16** and approximately 5–8% of uncharacterized materials based on peak areas of separated methyl and methoxyl peaks in the expanded spectrum.

Reduction of 16 to 9-(Hydroxymethyl)-7-methoxy-6-methyl-2,3,5,8-tetrahydro-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indole (18) and 6,9-Dimethyl-7-methoxy-2,3,5,8-tetrahydrodioxo-1*H*-pyrrolo[1,2-*a*]indole (20). To a stirred solution of **16** (9 mg, 0.03 mmol) in THF was added 5% Pd/C. A stream of hydrogen was passed over the mixture for 1.0 h (the organic phase turned colorless within 15 min) at which time a *clear* THF solution of LAH (0.50 mL of 1.2 M LAH, 0.60 mmol, 2000 mol %) was added. After 5 min, a heated bath (T_B = 80 °C) was applied for 5 min then replaced with an ice–water bath. After 20 min of cooling, the excess LAH was quenched with water, $FeCl_3$ (0.3 mL of 1 M $FeCl_3$ in 0.1 M HCl) was added min later, and 5 min later the mixture was diluted with dichloromethane (10 mL) and filtered. The solids were extracted with dichloromethane (10 mL), and the combined organic phase was washed with water (5 mL) and brine (5 mL) and dried, filtered, and evaporated to an orange solid (8.5 mg). NMR analysis of the expanded methyl and methoxyl regions showed **18** (94%) and **20** (6%). Chromatography (1 g of SiO_2 equilibrated with solvent I, sample applied in $CHCl_3$, eluted with solvent I to remove **20** and then ethyl acetate to remove **18**) provided **20** (0.2 mg, 6%) and **18** (7.0 mg, 90%).

18: mp 173–176 °C (lit.[4a] mp 170–173 °C, 180–182 °C); R_f (ethyl acetate) 0.41; NMR ($CDCl_3$) δ 1.97 (s, 3 H, CH_3), 2.56 (tt, 2 H, NCH_2CH_2), 2.83 (t, 2 H, $NCH_2CH_2CH_2$, J = 7.2 Hz), 3.99 (s, 3 H, OCH_3), 4.08 (t, 1 H, OH, J = 7.0 Hz), 4.21 (t, 2 H, NCH_2, J = 7.2), 4.59 (d, 2 H, CH_2OH, J = 7.0), IR (Nujol) 3546, 1656, 1639, 1608, 1495, 1314, 1272, 1203, 1167, 1096, 1049, 1014, 719 cm^{-1} (lit.[4a] IR 3559, 1664, 1653, 1610, 1099, 1053, 1018 cm^{-1} and 3460, 1684, 1650, 1605, 1105, 1022 cm^{-1}); UV λ_{max} 229 nm (ϵ 17 600), 285 (13 050), 353 (3400), 463 (1280) [lit.[4a] UV λ_{max} 230 nm (17 700), 287 (13 600), 350 (3340), 460 (1990)].

20: mp 164.5–167 °C; R_f (ethyl acetate) 0.63; NMR ($CDCl_3$) δ 1.94 (s, 3 H, quinone CH_3), 2.24 (s, 3 H, pyrrole CH_3), 2.54 (tt, 2 H, NCH_2CH_2), 2.77 (t, 2 H, $NCH_2CH_2CH_2$, J = 7 Hz), 3.98 (s, 3 H, OCH_3), 4.20 (t, 3 H, NCH_2, J = 7 Hz); IR ($CHCl_3$) 2941, 1658, 1637, 1608, 1475, 1431, 1366, 1316, 1277, 1193, 1109, 1005, 977 cm^{-1}; mass spectrum m/e (rel intensity) 247 (M + 2, 5.2), 246 (M + 1, 16.7), 245 (M^+, 100), 230 (36.2), 216 (21.7), 202 (36.1), 174 (20.0). Calcd for $C_{14}H_{15}NO_3$ m/e 245.1052, found m/e 245.1054 (M^+).

LAH Reduction of 16. Synthesis of 18 and 9-(Hydroxymethyl)-6-methyl-2,3,5,8-tetrahydro-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indole (19). To a stirred solution of **16** (16.0 mg, 0.053 mmol) in THF (9 mL) under N_2 was added a THF solution of LAH (0.30 mL of 1.5 M LAH, 0.45 mmol, 850 mol %) over the course of 5 min. After 7 h, water was added (~5 drops, until vigorous reaction ceased) followed 5 min later by $FeCl_3$ solution (0.6 mL of 1 M $FeCl_3$ in 0.1 M HCl) with rapid stirring. After 5 min the mixture was filtered, and the solids were extracted with dichloromethane (until the extracts were colorless). The combined organic phase was washed with water (5 mL) and brine (5 mL), dried, filtered, and evaporated to a red oil, 10.5 mg. NMR analysis shows a 60/40 mixture of **19**/**18** based on the clearly separated methyl absorptions. The NMR absorptions of **19** overlap with those of **18** with the exception of the following resonances.

19: NMR ($CDCl_3$) δ 2.07 (d, 3 H, CH_3, J = 1.5 Hz), 6.41 (q, 1 H, quinone H, J = 1.5 Hz).

Ethyl *N*-(2-Bromo-6-methoxy-5-methyl-1,4-benzoquinonyl)-(*E*)-α-2-pyrrolidinylideneacetate (21). To a stirred solution of hydroquinone **11** (20.0 mg, 0.052 mmol) in ether (5 mL) under an O_2 atmosphere was added saturated Na_2CO_3 solution (5 mL). After 4 h, ether (5 mL) was

(30) Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 227; **1974**, *96*, 8046.

added, and the layers were separated. The organic layer was washed with brine (2 × 3 mL), dried, and evaporated to provide **21** as a purple oil: 17.0 mg (85% yield, >99% by HPLC); R_f (ether) 0.65; R_t (column A, solvent B) 7.2 min; NMR ($CDCl_3$) δ 1.23 (t, 3 H, CH_2CH_3, J = 7 Hz); 1.98 (s, 3 H, quinone CH_3), 2.15 (br m, 2 H, NCH_2CH_2), 3.26 (m, 2 H, $NCH_2CH_2CH_2$), 3.62 (br t, 2 H, NCH_2, J = 8 Hz), 4.07 (s, 3 H, OCH_3), 4.08 (q, 2 H, CH_2CH_3), 4.40 (br s, 1 H, vinyl H); IR (neat) 2976, 1669, 1653 sh, 1613, 1587 cm^{-1}; mass spectrum *m/e* (rel intensity) 387, 386, 385, 384, 383 (6.7, 5.7, 27.9, 5.8, 22.0; M + 2^{81} Br, M + 1^{81} Br, M + 2^{79} Br + M^{+81}Br, M + 1^{79}Br, M^{+79}Br), 368, 370 (1.4, 2.0), 354, 356 (1.3, 1.5), 338, 340 (16.9, 16.6), 310, 312 (26.0, 22.7), 304 (100). Anal. Calcd for $C_{16}H_{18}NO_5Br$: C, 50.0; H, 4.7; N, 3.6. Found: C, 50.0; H, 4.9; N, 3.6.

8-Bromo-9a-[(ethoxycarbonyl)methyl]-1,2,3,6,7,9a-hexahydro-6,7-dioxopyrrolo[2,1-*b*]benzoxazole (23) from Treatment of 21 with Acid. To a stirred solution of quinone **21** (4.0 mg, 0.010 mmol) in chloroform (1 mL) was added *p*-toluenesulfonic acid monohydrate (1 mg) in $CHCl_3$ (1 mL). After 2 min, the color changed from purple to orange, and TLC showed conversion to a more polar orange spot. Evaporation gave a residue which was chromatographed on 0.5 g of SiO_2 (ether) to provide **23** as an orange solid: 3.1 mg (84%); mp 156–157 °C; R_f (ethyl acetate) 0.50; NMR ($CDCl_3$) δ 1.25 (t, 3 H, CH_2CH_3), 1.86 (s, 3 H, CH_3), 2.07, 2.25, 2.37, 2.53 (4 m, 1 H, each, $NCH_2CH_2CH_2$), 2.84, 3.02 (2 d, 1 H, 1 H, CH_2CO, J = 16 Hz), 3.94 (m, 2 H, NCH_2), 4.16 (q, 2 H, CH_2CH_3); IR (Nujol) 1745, 1647, 1610 cm^{-1}; mass spectrum *m/e* (rel intensity) 373, 371, 369 (13.4, 30.5, 15.9; M + 2^{81}Br, M + 2^{79}Br + M^{+81}Br, M^{+79}Br), 341, 343 (7.2, 7.0), 324, 326 (5.1, 6.5), 296, 298 (30.0, 28.6), 290 (59.3), 262 (38.5), 218 (71.8), 83 (100). Anal. Calcd for $C_{15}H_{16}NO_5Br$: C, 48.7; H, 4.4; N, 3.8. Found: C, 49.0; H, 4.4; N, 3.8.

$FeCl_3$ Oxidation of 11. Synthesis of 23 and Ethyl *N*-(2-Bromo-6-methoxy-5-methyl-1,4-benzoquinonyl)-3-oxo-6-aminocaproate (22). The oxidation procedure used to convert hydroquinone **28** to quinone **26** (see below) was scaled up 5× and applied to hydroquinone **11** (250 mg, 0.65 mmol). Isolation provided an oily red solid (228 mg) which was chromatographed on 23 g of SiO_2 (solvent **I**) to provide **22** (101 mg, 39%) and **23** (101 mg, 42%, identical with material prepared above).

22: red solid; mp 70–71 °C; R_f (ethyl acetate) 0.68; NMR ($CDCl_3$) δ 1.29 (t, 3 H, CH_2CH_3, J = 7.2 Hz), 1.89 (s, 3 H, CH_3), 1.97 (tt, 2 H, $=NCH_2CH_2$, J = 6.8, 7.2 Hz), 2.67 (t, 2 H, $NCH_2CH_2CH_2$, J = 6.8 Hz), 3.46 (s, 2 H, $COCH_2$), 3.82 (dt, 2 H, NCH_2, J = 7.2, 7.2 Hz), 4.13 (s, 3 H, OCH_3), 4.21 (q, 2 H, CH_2CH_3), 6.3 (br m, 1 H, NH); IR (Nujol) 3300, 1761, 1718, 1672, 1610, 1531 cm^{-1}. Anal. Calcd for $C_{16}H_{20}NO_6Br$: C, 47.8; H, 5.0; N, 3.5. Found: C, 48.1; H, 4.7; N, 3.6.

Conversion of 22 to 11. Quinone **22** (6.0 mg, 0.015 mmol) in chloroform (1.0 mL) was shaken with $Na_2S_2O_4$ solution (1.5 mL of a solution of 6 g of $Na_2S_2O_4$ in 25 mL of H_2O adjusted to pH 7.0 with 2 M NaOH). The red color disappeared after 10 min, and the layers were separated. The aqueous phase was extracted with chloroform (4 × 1 mL), and the combined organic phase was dried (Na_2SO_4), filtered, and evaporated to give **11** (5.8 mg, 100%), identical with material prepared above.

***N*-(2-Bromo-6-methoxy-5-methyl-1,4-benzoquinonyl)-4-aminobutyric Acid (24).** To a stirred solution of quinone **7** (20 mg, 0.065 mmol) in dimethylformamide (1.3 mL) was added 4-aminobutyric acid (13.3 mg, 0.129 mmol, 200 mol %). After 46 h the solvent was evaporated, and the residue was partitioned between water (5 mL) and chloroform (5 mL). The aqueous phase was extracted with chloroform (3 mL), and the combined organic phase was dried (Na_2SO_4), filtered, and evaporated to a purple solid (22.5 mg) which was recrystallized from methanol/water to give pure **24**: 16.1 mg (75%); red crystals, mp 151–152 °C; R_f (solvent I) 0.12; NMR ($CDCl_3$) δ 1.89 (s, 3 H, CH_3), 2.01 (tt, 2 H, NCH_2CH_2), 2.48 (t, 2 H, $NCH_2CH_2CH_2$, J = 7.2 Hz), 3.88 (dt, 2 H, NCH_2, J = 7, 6.8 Hz), 4.14 (s, 3 H, OCH_3), 6.3 (br m, 1 H, NH); IR (Nujol) 3356, 1704, 1656, 1595, 1508, 1404, 1289, 1255, 1208, 1157, 1110, 1099, 981, 794, 782, 751 cm^{-1}; mass spectrum *m/e* (rel intensity) 333, 331 (14.3, 14.1; M^{+81}Br, M^{+79}Br), 274, 272 (15.5, 17.6), 260, 258 (15.0, 15.2), 253 (19.8), 236 (20.7), 206 (17.3), 194 (36.9), 180 (24.4), 166 (31.0); exact mass calculated for $C_{12}H_{14}NO_5{}^{81}Br$ 333.0036, found *m/e* 333.0035 (M^+). Anal. Calcd for $C_{12}H_{14}NO_5Br \cdot {}^1/_4H_2O$: C, 42.8; H, 4.3; N, 4.2. Found: C, 42.8; H, 4.3; N, 4.1.

Conversion of 24 to 22.[21,22] To a stirred solution of **24** (30 mg, 0.09 mmol) in THF (0.45 mL) was added carbonyl diimidazole (17.6 mg, 0.108 mmol, 120 mol %). After 10 h the neutral magnesium salt of ethyl hydrogen malonate (28 mg, 0.10 mmol, 110 mol %) was added. After 17.5 h the solvent was evaporated, the residue was partitioned between ether (8 mL) and 1 M HCl (2 mL), the aqueous phase was extracted with ether (2 × 1 mL), and the combined organic phase was washed with saturated $NaHCO_3$ (2 mL), dried (Na_2SO_4), and evaporated to 34.4 mg of crude red **22**. Chromatography on 1 g SiO_2 (ether/hexane, 3/2) provided pure **22** (28.0 mg, 77%), identical with material prepared above.

Ethyl (*Z*)-2-Pyrrolidinylideneacetate (25).[23] NMR ($CDCl_3$) δ 1.25 (t, 3 H, CH_2CH_3, J = 7.1 Hz), 1.97 (tt, 2 H, NCH_2CH_2), 2.58 (t, 2 H, $NCH_2CH_2CH_2$, J = 7.8 Hz), 3.52 (t, 2 H, NCH_2, J = 6.9 Hz), 4.10 (q, 2 H, CH_2CH_3), 4.53 (s, 1 H, vinyl H), 7.9 (br, 1 H, NH); UV λ_{max} 206 nm (ϵ 3460), 279 (11 080); mp 62–63 °C (lit. mp 62–63 °C,[23] 63.0–63.5 °C[31]).

Addition of 25 to 7. Synthesis of Ethyl (*Z*)-α-(2-Bromo-6-methoxy-5-methyl-1,4-benzoquinonyl)-α-2-pyrrolidinylideneacetate (26) and Ethyl (*Z*)-α-(2-Bromo-5-methoxy-6-methyl-1,4-benzoquinonyl)-α-2-pyrrolidinylideneacetate (27). (A) With K_2CO_3. To a stirred solution of quinone **7** (50 mg, 0.16 mmol) in benzene (3.9 mL) was added vinylogous carbamate **25** (25 mg, 0.16 mmol) and K_2CO_3 (78 mg, 0.56 mmol, 350 mol %) in one portion. After 3 h, a 45 °C heating bath was applied. Monitoring the reaction by TLC showed a gradual consumption of starting materials and conversion to **26** and **27** [solvent I; **7** (R_f 0.59), **25** (0.36), **26** and **27** (0.28)]. After 23 h, reflux was initiated and K_2CO_3 (0.16 g) was added 18 h later followed by another addition (0.16 g) 10 h later. After an additional 13 h the mixture was filtered and evaporated to a dark purple oil which was chromatographed on 7.5 g of SiO_2 (solvent D) providing unreacted **7** (6 mg, 12%), **26** and **27** (25 mg, 40%, 92/8 by NMR), and **26** and **27** (92/8) contaminated with 3% of unreacted **25** (20 mg). As discussed below, **26** and **27** are best separated at their hydroquinone oxidation states.

(B) With NaH. A NaH/oil dispersion (44 mg of 50% dispersion, 0.90 mmol, 140 mol %) was washed with dry hexane and dried under nitrogen. Then THF (6.4 mL) was added followed by **25** (100 mg, 0.64 mmol). The mixture was stirred for an additional 15 min and then cooled in an ice bath. After 15 min quinone **7** (200 mg, 0.64 mmol) in THF (2 mL) was added dropwise over the course of 2 min. After a total of 15 min, the cold bath was removed, and 1 h later the reaction mixture was filtered and evaporated to a purple oil. Chromatography on 30 g of SiO_2 (solvent C) yielded unreacted **7** (10 mg, 5%) and a mixture of **26** and **27** (202 mg, 81%, 85/15 by NMR). Anal. Calcd for $C_{16}H_{18}NO_5Br$: C, 50.0; H, 4.7; N, 3.6. Found: C, 50.3; H, 4.9; N, 3.5. Properties of pure **26** and **27** are listed below.

Reduction of 26 and 27 to Ethyl (*Z*)-2-Bromo-3,6-dihydroxy-4-methoxy-5-methyl-α-2-pyrrolidinylidenebenzeneacetate (28) and Ethyl (*Z*)-2-Bromo-3,6-dihydroxy-5-methoxy-4-methyl-α-2-pyrrolidinylidenebenzeneacetate (29). To a mixture of bromoquinones **26** and **27** (202 mg, 0.52 mmol, prepared by method B) in ether (4 mL) was added $Na_2S_2O_4$ solution (0.83 g of $Na_2S_2O_4$ in 4 mL of water, taken to pH 7.0 with 2 M NaOH). The mixture was rapidly shaken until the purple color was bleached (~5 min), and the organic phase was stored over Na_2SO_4 under N_2. The aqueous phase was extracted with chloroform (5 × 4 mL) which was added to the ether. Filtration and evaporation provided a residue which was immediately dissolved in chloroform and chromatographed on 25 g of SiO_2 (solvent D) to give recovered **26** and **27** (1.2 mg, 0.6%, partial oxidation on column), hydroquinone **28** (161 mg, 79%), hydroquinone **29** (25 mg, 12%), and a mixture of **28** and **29** (4 mg, 2%).

28: mp 155–156 °C with dec; R_f (solvent **I**) 0.20; NMR ($CDCl_3$) δ 1.16 (dd, 3 H, CH_2CH_3, J = 7, 7 Hz), 1.98 (br tt, 2 H, NCH_2CH_2), 2.29, 2.27 (2 overlapping t, 1 H each, $NCH_2CH_2CH_aH_b$, J_{a-CH_2} = 8 Hz, J_{b-CH_2} = 8 Hz, J_{ab} = ~0 Hz), 3.65 (t, 2 H, NCH_2, J = 7 Hz), 3.84 (s, 3 H, OCH_3), 4.02 (dq, 1 H, $CHHCH_3$, J = 7 Hz, J_{gem} = 11 Hz), 4.18 (dq, 1 H, $CHHCH_3$, J = 7, 11 Hz), 5.20, 5.40 (2 s, 1 H each, 2 OH), 8.7 (br, 1 H, NH); IR (thin film) 3401, 2994, 1653, 1587 cm^{-1}. Anal. Calcd for $C_{16}H_{20}NO_5Br$: C, 49.8; H, 5.2; N, 3.6. Found: C, 49.7; H, 5.2; N, 3.6.

29: mp 153–154 °C; R_f (solvent I) 0.13; NMR ($CDCl_3$) δ 1.15 (dd, 3 H, CH_2CH_3, J = 7, 7 Hz), 1.95 (br tt, 2 H, NCH_2CH_2), 2.26 (s, 3 H, CH_3), 2.31, 2.32 (2 overlapping t, 1 H each, $NCH_2CH_2CH_aH_b$, J_{a-CH_2} = 8 Hz, J_{b-CH_2} = 8 Hz, J_{ab} ~ 0 Hz), 3.64 (t, 2 H, NCH_2, J = 7 Hz), 3.82 (s, 3 H, OCH_3), 4.06 (dq, 1 H, $CHHCH_3$, J = 7 Hz, J_{gem} = 11 Hz), 4.15 (dq, 1 H, $CHHCH_3$, J = 7, 11 Hz), 5.13, 5.25 (2 s, 1 H each, 2 OH), 8.6 (br, 1 H, NH); IR ($CHCl_3$) 3507, 3030, 1658, 1585 cm^{-1}. Anal. Calcd for $C_{16}H_{20}NO_5Br$: C, 49.8; H, 5.2; N, 3.6. Found: C, 49.8; H, 5.2; N, 3.7.

Oxidation of Hydroquinone 28 to Quinone 26. To a stirred solution of **28** (50 mg, 0.13 mmol) in methanol (5 mL) was added $FeCl_3$ solution (2.5 mL of a solution of 2.70 g $FeCl_3 \cdot 6H_2O$ in 20 mL of 0.1 M HCl). After 5 min, water (10 mL) was added and the mixture was extracted with dichloromethane (3 × 2 mL). The combined organic phase was washed (4 mL of brine), dried, and evaporated to **26** as an oily solid: 50 mg (100%); R_f (solvent I) 0.28; NMR ($CDCl_3$) δ 1.15 (t, 3 H, CH_2CH_3, J = 7.1 Hz), 1.99 (masked m, 2 H, NCH_2CH_2), 1.99 (s, 3 H, CH_3), 2.33

(31) Horri, Z.-I.; Morikawa, K.; Ninomiya, I. *Chem. Pharm. Bull.* **1969**, *17*, 2230.

(ddd, 1 H, NCH_2CH_2CHH, J = 7, 7, 16 Hz), 2.54 (ddd, 1 H, NCH_2CH_2CHH, J = 7, 7, 16 Hz), 3.61 (m, 2 H, NCH_2), 4.05 (s, 3 H, OCH_3), 4.07 (q, 2 H, CH_2CH_3), 8.7 (br, 1 H, NH); IR (neat) 3378, 2985, 1658, 1582 cm^{-1}; mass spectrum m/e (rel intensity) 387 (3.5, M + ^{81}Br), 385 (8.3, M + ^{79}Br and M^+ ^{81}Br), 383 (5.0, M^+ ^{79}Br, 341, 339 (8.8, 8.9), 326, 324 (19.4, 19.7), 304 (100), 276 (82.1), 258 (18.9), 246 (11.0), 230 (10.9).

Air Oxidation of Hydroquinone 29 to Quinone 27. A 15-mg sample of **29** partially air oxidized over the course of ~1 month. Purification of **29** (1 g of SiO_2: solvent I) provided a small sample of pure **27**: R_f (solvent I) 0.28; NMR ($CDCl_3$) δ 1.16 (t, 3 H, CH_2CH_3, J = 7 Hz), 2.00 (s, 3 H, CH_3), 2.0 (masked m, 2 H, NCH_2CH_2), 2.31 (ddd, 1 H, NCH_2CH_2CHH, J = 8, 8, 17 Hz), 2.62 (ddd, 1 H, NCH_2CH_2CHH, J = 8, 8, 17 Hz), 3.62 (m, 2 H, NCH_2), 4.01 (s, 3 H, OCH_3), 4.06 (q, 2 H, CH_2CH_3), 8.7 (br, 1 H, NH); IR (neat) 3325, 1675, 1661, 1650, 1591, 1573 cm^{-1}.

Metal-Catalyzed Cyclization of Hydroquinone 29 to Indoloquinone 16. To a stirred solution of **29** (8.0 mg, 0.02 mmol) in acetonitrile (0.42 mL) were added K_2CO_3 (9.0 mg, 0.6 mmol, 320 mol %) and $CuBr_2$ (1.0 mg, 0.005 mmol, 20 mol %). Oxidation to purple **27** was seen within minutes. After 11 h the yellow mixture was filtered and evaporated. The residue was dissolved in chloroform, filtered, and evaporated to give **16** as a yellow solid (6.3 mg, 98%), identical with the material prepared above.

Metal-Catalyzed Cyclization of Hydroquinone 28 to Indoloquinone 30. The above reaction was repeated on the same scale using hydroquinone **28**. Isolation after 4.5 h gave **30**: 6.3 mg (98%), mp 157-159 °C; R_f (solvent I) 0.56; R_t (column A, solvent G, 2 mL/min) 23.7; NMR ($CDCl_3$) 1.38 (t, 3 H, CH_2CH_3, J = 7.1 Hz), 2.01 (s, 3 H, CH_3), 2.60 (tt, 2 H, NCH_2CH_2), 3.12 (t, 2 H, $NCH_2CH_2CH_2$, J = 7.6), 3.97 (s, 3 H, OCH_3), 4.31 (masked t, 2 H, NCH_2, J = 7.4 Hz), 4.34 (q, 2 H, CH_2CH_3); IR ($CHCl_3$) 2985, 1727, 1695, 1661, 1616, 1504, 1374, 1319, 1302, 1200, 1129, 1096, 1009, 933 cm^{-1}. Anal. Calcd for $C_{16}H_{17}NO_5$: C, 63.3; H, 5.6; N, 4.6. Found: C, 63.2; H, 5.8; N, 4.6.

Addition of Vinylogous Carbamate 25 to Quinone 7 in the Presence of Copper. Ring Closure to Indoloquinone 3 Esters 16 and 30. To a rapidly stirred solution of **7** (50 mg, 0.16 mmol) and **25** (25 mg, 0.16 mmol) in acetonitrile (2 mL) were added K_2CO_3 (78 mg, 0.56 mmol, 350 mol %), and $CuBr_2$ (3.6 mg, 0.016 mmol, 10 mol %). After 5 days, the mixture was filtered and evaporated to a yellow solid (50 mg, 102%). NMR ($CDCl_3$) analysis showed **16** and **30** in a ratio of 5/95. Preparative MPLC (solvent H) of 10 mg of the mixture gave base-line separation of **16** and **30** and a recovery of 9 mg of **30**.

Registry No. 4, 2207-57-0; **7**, 77357-44-9; **8**, 85096-93-1; **9**, 85083-28-9; **10**, 85083-29-0; (*E*)-**11**, 85083-30-3; **12a**, 85083-31-4; **12b**, 85083-32-5; (*E*)-**13**, 85096-94-2; **14**, 85083-33-6; (*E*)-**15**, 85083-34-7; **16**, 83605-97-4; **17**, 83605-95-2; **18**, 3188-26-9; **19**, 29769-40-2; **20**, 66865-11-0; (*E*)-**21**, 85083-35-8; **22**, 85083-36-9; **23**, 85083-37-0; **24**, 85083-38-1; (*Z*)-**25**, 35150-22-2; (*Z*)-**26**, 85083-39-2; (*Z*)-**27**, 85083-40-5; (*Z*)-**28**, 85083-41-6; (*Z*)-**29**, 85083-42-7; **30**, 85083-43-8; $Mg(O_2CCH_2CO_2C_2H_5)_2$, 37517-78-5; 2-methoxy-3-methylhydroquinone, 1760-80-1; 2,3-dibromo-5-methoxy-6-methylhydroquinone, 77357-50-7; homoproline ethyl ester acetate salt, 72866-98-9; 4-aminobutyric acid, 56-12-2.

Nitric Oxide Ferrohemes: Kinetics of Formation and Photodissociation Quantum Yields

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Abstract: The quantum yield for NO photodissociation from iron protoporphyrin 1-methylimidazole nitrosyl, FePP(1-MeIm)(NO), in the presence of excess 1-MeIm is wavelength independent, Φ_1 = 0.08-0.1, and the NO binding rate to the five-coordinate heme, Fe(PP)(1-MeIm), is $k_5^{NO} = 1.7 \pm 0.7 \times 10^8$ M^{-1} s^{-1}; for Fe(PP)(NO), Φ_1 = 0.05-0.08. This quantum yield is much higher than believed earlier but nevertheless appears to be significantly less than unity; the result is important to an understanding of heme-ligand photodissociation. In contrast for myoglobin and T- and R-state hemoglobin, $k_5 = 1.8 \times 10^7$ M^{-1} s^{-1} and $\Phi_1 = 10^{-3}$. The observations for model systems and proteins (and comparable results for CO) can be understood self-consistently within a scheme for ligand binding and photorelease that incorporates as an intermediate a (heme, ligand) encounter pair, in the one case surrounded by a solvent cage and in the other embedded in the heme pocket of a protein. At ambient temperature, dissociation of a (heme model, NO) encounter pair in solution is several times more likely than bond formation. In contrast, because diffusion into and out of the protein heme pocket is restricted, a NO molecule in the pocket is over 100 times more likely to bind than to escape.

We have employed flash photolytic techniques to measure the quantum yields for NO photodissociation from nitrosylferroheme model compounds and the rate constant for NO binding to the five-coordinate $Fe^{II}PP$(1-MeIm).[1] Comparisons between results for model compounds and those for hemoproteins are particularly useful in examining the mechanisms by which the properties of the heme group are modulated by a protein environment.[2-4] The binding of NO by ferrohemoproteins is anomalous in a number of respects. Although cooperatively is shown in the binding of O_2 and CO to Hb,[5] the association of NO is noncooperative.[6,7] The kinetics of CO binding to R- and T-state Hb exhibits allosteric differentiation, with further differentiation in Mb,[8,9] but all three binding rates are identical for NO.[7,10] Finally, the binding rate of CO to unconstrained model hemes is identical with that of R-state hemoglobin,[11,9] whereas a preliminary report by Morris and Gibson suggests that the rate of NO binding in the protein is depressed.[10] We find that both the NO photodissociation quantum yield and binding rates for the heme model FePP(1-

(1) Abbreviations: FePP, ferrous protoporphyrin(IX); 1-MeIm, 1-methylimidazole; Hb, hemoglobin; T, low affinity; R, high affinity; Mb, myoglobin; CTAB, cetyltrimethylammonium bromide; L, diatomic ligand; B, nitrogenous base.

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